PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/007622	12.03.2004	12.03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/18

Applicant
GENENTECH, INC.

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1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-45,49-71

because:

☒ the said international application, or the said claims Nos. 1-45,49-71 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-45, 49-71
	No:	Claims	46-48
Inventive step (IS)	Yes:	Claims	1-45,49-71
	No:	Claims	46-48
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	see separate sheet

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Concerning section III

Claims 1-45, 49-71 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Concerning section V

1. The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: LECOUTER JENNIFER ET AL: "Endocrine gland-derived VEGF and the emerging hypothesis of organ-specific regulation of angiogenesis" NATURE MEDICINE, vol. 8, no. 9, September 2002 (2002-09), pages 913-917, XP002293706 ISSN: 1078-8956

   D2: WECHSELBERGER C ET AL: "The mammalian homologues of frog Bv8 are mainly expressed in spermatocytes" FEBS LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 462, no. 1-2, 26 November 1999 (1999-11-26), pages 177-181, XP004260611 ISSN: 0014-5793

   D3: LECOUTER JENNIFER ET AL: "Identification of an angiogenic mitogen selective for endocrine gland endothelium" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 412, no. 6850, 30 August 2001 (2001-08-30), pages 877-884, XP002194811 ISSN: 0028-0836

   D4: WO 02/00711 A (GENENTECH INC) 3 January 2002 (2002-01-03)

   D5: WO 03/020892 A (FERRARA NAPOLEONE ; GENENTECH INC (US); LE COUTER JENNIFER (US)) 13 March 2003 (2003-03-13)

   Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. The document D1 discloses Bv8 and EG-VEGF as belonging to a group of proteins and having a high degree of homology. These proteins are not structurally related to VEGF. They have been shown to be expressed mainly in steroidogenic glands, ovary, testis, and to regulate proliferation and differenciation of vascular steroidogenic endothelial cells.

The prior art neither discloses nor suggests their expression in bone marrow cells, nor their ability to promote B/T cell proliferation, cytokine production, recovery after myelopsuppression, as shown by the present application.
Hence the subject-matter of claims 1-45 and 49-71 is novel and inventive.

The document D4 discloses pharmaceutical compositions comprising EG-VEGF. The instructions for use do not confer novelty to a first medical use claim, hence the subject-matter of claims 46-48 is not novel.

3. For the assessment of the present claims 1-45, 49-71 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Concerning section VI

The document D5, published after the priority date of the present application, could be relevant for the question of novelty upon entry in the regional phase, as it discloses pharmaceutical compositions comprising Bv8. The instructions for use do not confer novelty to a first medical use claim, hence the subject-matter of claims 46-48 would not be novel over D5.